1. NAME OF THE MEDICINAL PRODUCT

Bramitob 300mg/4ml Nebuliser Solution.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 4 ml single-dose container contains tobramycin 300 mg.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Nebuliser solution.

Clear, yellowish solution.

4.1 Therapeutic indications

Management of chronic pulmonary infection due to *Pseudomonas aeruginosa* in patients with cystic fibrosis aged 6 years and older.

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

4.2 Posology and method of administration

Bramitob is intended for inhalation only and not for parenteral use.

Therapy should be initiated by a physician experienced in the management of cystic fibrosis.
The recommended dose for adults and children above 6 years is one single-dose container (300mg) twice daily (morning and evening) for 28 days. The dose interval should be as close as possible to 12 hours. After 28 days of therapy with Bramitob, patients should stop treatment for the next 28 days. Alternate cycles of 28-days of active therapy followed by 28 days without treatment should be maintained (a cycle of 28 days with therapy and 28 days without treatment).

Children under 6 years old
The efficacy and safety of Bramitob have not been demonstrated in patients less than 6 years of age.

Elderly patients
Tobramycin should be used with caution in elderly patients who may have reduced renal function (see section 4.4).

Patients with renal impairment
Tobramycin should be used with caution in patients with known or suspected renal dysfunction. Bramitob should be discontinued in the case of nephrotoxicity until serum concentration of tobramycin fall below 2 µg/mL (see section 4.4).

Patients with hepatic insufficiency
No changes in Bramitob dose are required in hepatic insufficiency.

Dosage is not adjusted for body weight. All patients should be administered one single-dose container of Bramitob (300 mg of tobramycin) twice daily.

Treatment with tobramycin should be continued on a cyclical basis for as long as the physician considers the patient is gaining clinical benefit from the inclusion of Bramitob in their treatment regimen. If clinical deterioration of pulmonary status is evident, additional anti-pseudomonal therapy should be considered.

Method of Administration:

The single-dose container should be opened just before use. Any unused solution that is not immediately used should be discarded and not stored for re-use.

Administration of Bramitob should be carried out following general hygienic standards. The apparatus used should be clean and working correctly; the nebuliser, that should be for personal use only, should be kept clean and regularly disinfected.

For cleaning and disinfection of the nebuliser, refer to the instructions provided with the nebuliser.

Maximum tolerated daily dose:
The maximum tolerated daily dose of Bramitob has not been established.

Instructions for opening the container:

1) Bend the single-dose container in both directions
2) Detach the single-dose container from the strip, firstly above then in the middle
3) Open the single-dose container by rotating the flap as indicated by the arrow
4) Exerting a moderate pressure on the single-dose container's walls, let the medicinal product flow into the glass tube of the nebuliser.

The contents of one single-dose container (300mg) emptied into the nebuliser, should be administered by inhalation over approximately a 15-minute period using a PARI LC PLUS reusable nebuliser equipped with PARI TURBO BOY compressor (drug delivery rate 6.2 mg/min, total drug delivery 92.8 mg, mass median aerodynamic diameter: D_{10} 0.65 µm, D_{50} 3.15µm, D_{90} 8.99µm) or PARI LC SPRINT equipped with compressor PARI BOY Sx (drug delivery rate 6.7 mg/min, total drug delivery 99.8 mg, mass median aerodynamic diameter: D_{10} 0.70 µm, D_{50} 3.36µm, D_{90} 9.41µm)

Bramitob is inhaled while the patient is sitting or standing upright and breathing normally through the mouthpiece of the nebuliser. Nose clips may help the patient with breathing through the mouth. The patient should continue their standard regimen of chest physiotherapy. The use of appropriate bronchodilators should continue as thought clinically necessary. In patients receiving several different respiratory therapies, it is recommended that they are taken in the following order: bronchodilator, respiratory physiotherapy, other inhaled medicinal products, and finally Bramitob.

Bramitob should not be mixed with other inhalation medicinal products.

4.3 Contraindications

Administration of Bramitob is contraindicated in all patients with hypersensitivity to tobramycin, to any other aminoglycosides or to any of the excipients listed in section 6.1.
It is also contraindicated in patients receiving potent diuretics, such as furosemide or ethacrynic acid, which have proved to be ototoxic.

4.4 Special warnings and precautions for use

General Warnings

Tobramycin should be used with caution in patients with known or suspected renal, auditory, vestibular or neuromuscular dysfunction, or with severe, active haemoptysis.
Renal and eighth cranial nerve function should be closely monitored in patients with known or suspected renal impairment and also in those whose renal function is initially normal but who develop signs of renal dysfunction during therapy. Evidence of impairment in renal, vestibular and/or auditory function requires discontinuation of the drug or dosage adjustment.
The serum concentration of tobramycin should only be monitored through venipuncture and not finger prick blood sampling which is a non validated dosing method. It has been observed that contamination of the skin of the fingers from the preparation and nebulisation of tobramycin may lead to falsely increased serum levels of the drug. This contamination cannot be completely avoided by hand washing before testing.

Bronchospasm
Bronchospasm can occur following inhalation of medicinal products and has been reported with nebulised tobramycin. The first dose of Bramitob should be given under medical supervision, using a pre-nebulisation bronchodilator if this is already part of the current treatment regimen for the patient. FEV_1 (forced expiratory volume) should be measured before and after nebulisation. If there is evidence of therapy-induced bronchospasm in a patient not receiving a bronchodilator, the test should be repeated on a separate occasion, using a bronchodilator. Onset of bronchospasm in the presence of bronchodilator therapy may indicate an allergic reaction. Should an allergic reaction be suspected, Bramitob should be discontinued. Bronchospasm should be treated as clinically appropriate.

Neuromuscular disorders
Tobramycin should be used with great caution in patients with neuromuscular disorders, such as parkinsonism or other conditions characterised by myasthenia, including myasthenia gravis, as aminoglycosides may worsen muscular weakness due to a potential curare-like effect on the neuromuscular function.

Nephrotoxicity
Although nephrotoxicity has been associated with parenteral aminoglycoside therapy, there was no evidence of nephrotoxicity during clinical trials with tobramycin. The product should be used with caution in patients with known or suspected renal dysfunction and tobramycin serum concentrations should be monitored, e.g. serum level assays after two or three doses should be performed, so that the dosage could be adjusted if necessary, and also at three to four day intervals during therapy. In the event of changing renal function, more frequent serum levels should be obtained and the dosage or dosage intervals adjusted. Patients with severe renal impairment, i.e. serum creatinine > 2 mg/dl (176.8 µmol/l) were not included in the clinical studies.
Current clinical practice recommends that baseline renal function should be assessed. Furthermore, the renal function should be periodically reassessed, by regularly monitoring urea and creatinine levels at least every 6 full cycles of therapy with tobramycin (180-day treatment with nebulised tobramycin). If there is evidence of nephrotoxicity, therapy with tobramycin should be discontinued until the drug minimum serum concentrations fall below 2 µg/ml. Tobramycin therapy may then be resumed following medical advice. Patients receiving concomitant parenteral aminoglycoside therapy should be strictly monitored, due to the risk of cumulative toxicity.
Monitoring of renal function is particular important in elderly patients who may have reduced renal function that may not be evident in the results of routine screening tests, such as blood urea or serum creatinine. A creatinine clearance determination may be more useful.
Urine should be examined for increased excretion of protein, cells and casts. Serum creatinine or creatinine clearance (preferred over blood urea) should be measured periodically.

Ototoxicity
Ototoxicity, manifested as both auditory and vestibular toxicity has been reported with the parenteral aminoglycosides. Vestibular toxicity may be manifested by vertigo, ataxia or dizziness.
During controlled clinical studies with tobramycin, modest hypoacusia and vertigo were observed, while with other nebulised tobramycin containing medicines auditory toxicity, as measured by

complaints of hearing loss or by audiometric evaluations did not occur during controlled clinical studies.
In open label studies and post-marketing experience, some patients with a history of prolonged previous or concomitant use of intravenous aminoglycosides have experienced hearing loss.
The physician should consider the possibility that aminoglycosides may cause vestibular and cochlear toxicity and should assess auditory function throughout the treatment period with Bramitob. In patients with a predisposing risk due to previous prolonged systemic therapy with aminoglycosides, it may be necessary to consider audiological assessment before starting therapy with tobramycin. The occurrence of tinnitus warrants caution, since it represents an ototoxic symptom. If the patient reports about tinnitus or hearing loss during the therapy with aminoglycosides, the physician should consider whether audiologic tests are necessary. When feasible, it is recommended that serial audiograms are performed in patients on continuous therapy, which are at particular high risk of ototoxicity. Patients receiving concomitant parenteral therapy with aminoglycosides should be monitored as clinically appropriate, taking into account the risk of cumulative toxicity.

Haemoptysis
Inhalation of nebulised solutions may induce a cough reflex. The use of nebulised Bramitob in patients with active, severe haemoptysis should be undertaken only if the benefits of treatment are considered to outweigh the risks of inducing further haemorrhage.

Microbial Resistance
In clinical studies, some patients treated with nebulised tobramycin showed an increase in aminoglycoside Minimum Inhibitory Concentrations for P. aeruginosa isolates tested. There is a theoretical risk that patients being treated with nebulised tobramycin may develop P. aeruginosa isolates resistant to intravenous tobramycin (see section 5.1 Pharmacodynamic properties). In clinical trials there is no data in patients with Burkholderia cepacia infections.

For information related to administration during pregnancy and lactation see section 4.6 “Pregnancy and lactation”.

4.5 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

Concurrent and/or sequential use of Bramitob with other medicinal products with nephrotoxic or ototoxic potential should be avoided. Some diuretics can enhance aminoglycoside toxicity by altering antibiotic concentrations in serum and tissue. Bramitob should not be administered concomitantly with furosemide, ethacrynic acid, urea or intravenous and oral mannitol.

Other medicinal products that have been reported to increase the potential toxicity of parenterally administered aminoglycosides include:
Amphotericin B, cephalotin, ciclosporin, tacrolimus, polymyxins (risk of increased nephrotoxicity); platinum compounds (risk increased nephrotoxicity and ototoxicity).
Anticholinesterases, botulinum toxin: Due to their neuromuscular effects, the combination with tobramycin should be avoided.

Others:
In clinical studies, patients taking nebulised tobramycin concomitantly with dornase alfa, mucolytic, B agonists, inhaled corticosteroids, and other oral or parenteral anti-pseudomonal antibiotics, showed adverse events similar to the patients of the control group.

4.6 Fertility, pregnancy and lactation

Bramitob should not be used during pregnancy or lactation unless the benefits to the mother outweigh the risks to the foetus or baby.

Pregnancy

There are no adequate data from the use of tobramycin administered by inhalation in pregnant women. Animal studies do not indicate a teratogenic effect of tobramycin (see section 5.3 Preclinical data). However, aminoglycosides can cause foetal harm (e.g., congenital deafness) when high systemic concentrations are achieved in a pregnant woman. If Bramitob is used during pregnancy, or if the patient becomes pregnant while taking Bramitob, she should be informed of the potential hazard to the foetus.

Lactation

Systemic tobramycin is excreted in breast milk. It is not known if inhaled tobramycin will result in serum concentrations high enough for tobramycin to be detected in breast milk. Because of the potential risk for ototoxicity and nephrotoxicity with tobramycin in infants, a decision should be made whether to terminate nursing or discontinue Bramitob therapy.

4.7 Effects on ability to drive and use machines

No studies on the effect on the ability to drive and use machines have been performed. On the basis of reported adverse drug reactions, tobramycin is presumed to be unlikely to produce an effect on ability to drive and use machinery.

Nevertheless, since dizziness and/or vertigo may occur, patients who are going to drive or use machinery should be alerted.

4.8 Undesirable effects

In controlled clinical trials (4) and uncontrolled clinical trials (1) with Bramitob (565 patients treated), the most common reactions were those concerning the respiratory tract (cough and dysphonia).

The adverse reactions reported in the clinical trials (see below) are classified as: common (≥1/100 and <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 and <1/1,000); very rare (<1/10,000).

System Organ Class	***Adverse Reaction***	***Frequency***
Infections & Infestations	*Fungal infection, oral candidiasis*	*Uncommon*
Nervous system disorders	*Headache*	*Uncommon*
Ear and labyrinth disorders	*Vertigo, hypoacusis, deafness neurosensory (see section 4.4)*	*Uncommon*
Respiratory, thoracic and mediastinal disorders	*Cough, dysphonia*	*Common*
	Forced expiratory volume decreased, dyspnoea, rales, haemoptysis, oropharyngeal pain, productive cough	*Uncommon*
Gastrointestinal disorders	*Salivary hypersecretion, glossitis, abdominal pain upper, nausea*	*Uncommon*
Skin and subcutaneous tissue disorders	*Rash*	*Uncommon*
General disorders and administration site conditions	*Asthenia, chest discomfort, mucosal dryness*	*Uncommon*
Investigations	*Transaminases increased*	*Uncommon*

In controlled clinical trials with other nebulised tobramycin containing medicines, dysphonia and tinnitus were the only undesirable effects reported in significantly more patients treated with tobramycin; (13%

tobramycin vs. 7% control) and (3% tobramycin vs. 0% control) respectively. These episodes of tinnitus were transient and resolved without discontinuation of tobramycin therapy, and were not associated with permanent loss of hearing on audiogram testing. The risk of tinnitus did not increase with repeated cycles of exposure to tobramycin.

Additional undesirable effects, some of which are common sequelae of the underlying disease, but where a causal relationship to tobramycin could not be excluded were: sputum discoloured, respiratory tract infection, myalgia, nasal polyps and otitis media.

In addition, cumulative post-marketing data with products containing nebulised tobramycin reported the following adverse reactions (same frequency classification reported above):

System Organ Class	***Adverse Reaction***	***Frequency***
Infections & Infestations	*Laryngitis*	*Rare*
	Fungal infection, oral candidiasis	*Very rare*
Blood and lymphatic system disorders	*Lymphadenopathy*	*Very rare*
Immune system disoders	*Hypersensitivity*	*Very rare*
Metabolism and nutrition disorders	*Anorexia*	*Rare*
Nervous system disorders	*Dizziness, headache, aphonia*	*Rare*
	Somnolence	*Very rare*
Ear and labyrinth disorders	*Tinnitus, hearing loss (see section 4.4)*	*Rare*
	Ear disorders, ear pain	*Very rare*
Respiratory, thoracic and mediastinal disorders	*Cough, pharyngitis, dysphonia, dyspnoea*	*Uncommon*
	Bronchospasm, chest discomfort, lung disorder, haemoptysis, epistaxis, rhinitis, asthma, productive cough	*Rare*
	Hyperventilation, hypoxia, sinusitis	*Very rare*
Gastrointestinal disorders	*Dysgeusia, mouth ulceration vomiting, nausea*	*Rare*
	Diarrhoea, abdominal pain	*Very rare*
Skin and subcutaneous tissue disorders	*Rash*	*Rare*
	Urticaria, pruritus	*Very rare*
Musculo-skeletal, connective tissue and bone disorders	*Back pain*	*Very rare*
General disorders and administration site conditions	*Asthenia, pyrexia, chest pain, pain, nausea*	*Rare*
	Malaise	*Very rare*
Investigations	*Pulmonary function test decreased*	*Rare*

In open label studies and post-marketing experience, some patients with a history of prolonged previous or concomitant use of intravenous aminoglycosides have experienced hearing loss (see 4.4).

Parenteral aminoglycosides have been associated with hypersensitivity, ototoxicity and nephrotoxicity (see sections 4.3 "Contraindications" and 4.4 "Special warnings and precautions for use").

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via:
Yellow Card Scheme Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Symptoms

Administration by inhalation results in low systemic bioavailability of tobramycin. Symptoms of aerosol overdose may include severe hoarseness.

In the event of accidental ingestion of Bramitob, toxicity is unlikely as tobramycin is poorly absorbed from an intact gastrointestinal tract.

In the event of inadvertent intravenous administration of Bramitob, signs and symptoms of parenteral tobramycin overdose may occur, such as dizziness, tinnitus, vertigo, hearing loss, respiratory distress and/or neuromuscular blockade and renal impairment.

Treatment

Acute toxicity should be treated with immediate withdrawal of Bramitob, and baseline tests of renal function should be carried out. Tobramycin serum concentrations may be helpful in monitoring overdose. In case of any overdose, the possibility of drug interactions with alterations in the elimination of Bramitob or other medicinal products should be considered.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Aminoglycoside antibacterials, ATC code: J01GB01.

Tobramycin is an aminoglycoside antibiotic produced by Streptomyces tenebrarius. It acts primarily by disrupting protein synthesis leading to altered cell membrane permeability, progressive disruption of the cell envelope and eventual cell death. It is bactericidal at concentrations equal to or slightly greater than inhibitory concentrations.

Breakpoints

Established susceptibility breakpoints for parenteral administration of tobramycin are inappropriate in the aerosolised administration of the medicinal product. Cystic fibrosis (CF) sputum exhibits an inhibitory action on the local biological activity of nebulised aminoglycosides. This necessitates sputum concentrations of aerosolised tobramycin to be some ten and twenty–five fold above the Minimum Inhibitory Concentration (MIC) for, respectively, P. aeruginosa growth suppression and bactericidal activity. In controlled clinical trials, 90% of patients receiving tobramycin achieved sputum concentrations 10 fold the highest P. aeruginosa MIC cultured from the patient, and 84% of patients receiving tobramycin achieved 25 fold the highest MIC. Clinical benefit is still achieved in a majority of patients who culture strains with MIC values above the parenteral breakpoint.

Susceptibility

In the absence of conventional susceptibility breakpoints for the nebulised route of administration, caution must be exercised in defining organisms as susceptible or insusceptible to nebulised tobramycin.

In clinical studies with inhaled tobramycin, most patients (88%) with P. aeruginosa isolates with tobramycin MICs <128 µg/mL at baseline showed improved lung function following treatment with

tobramycin. Patients with a P. aeruginosa isolate with a MIC ≥128 µg/mL at baseline are less likely to show a clinical response.

Based upon in vitro data and/or clinical trial experience, the organisms associated with pulmonary infections in CF may be expected to respond to tobramycin therapy as follows:

Susceptible	Pseudomonas aeruginosa Haemophilus influenzae Staphylococcus aureus
Insusceptible	Burkholderia cepacia Stenotrophomonas maltophilia Alcaligenes xylosoxidans

Treatment with tobramycin regimen in clinical studies showed a small but clear increase in tobramycin, amikacin and gentamicin Minimum Inhibitory Concentrations for P. aeruginosa isolates tested. Each additional 6 months of treatment resulted in incremental increases similar in magnitude to that observed in the 6 months of controlled studies. The most prevalent aminoglycoside resistance mechanism seen in P. aeruginosa isolated from chronically infected CF patients is impermeability, defined by a general lack of susceptibility to all aminoglycosides. P. aeruginosa isolated from CF patients has also been shown to exhibit adaptive aminoglycoside resistance that is characterised by a reversion to susceptibility when the antibiotic is removed.

Other Information

In controlled clinical studies, treatment with Bramitob carried out according to alternate cycles as described above, led to an improvement in lung function, with results maintained above baseline throughout therapy and 28 day periods off therapy.

In clinical trials with tobramycin there are no data in patients aged less than 6 years.

There is no evidence that patients treated with up to 18 months with tobramycin were at a greater risk for acquiring B. cepacia, S. maltophilia or A. xylosoxidans, than would be expected in patients not treated with tobramycin. Aspergillus species were more frequently recovered from the sputum of patients who received tobramycin; however, clinical sequelae such as Allergic Bronchopulmonary Aspergillosis (ABPA) were reported rarely and with similar frequency as in the control group.

5.2 Pharmacokinetic properties

Absorption and distribution

Following oral administration only 0.3-0.5% of the drug appears in urine to prove systemic absorption. After administration via nebuliser in 6 cystic fibrosis patients, mean absolute bioavailability was about 9.1% of the dose. Systemic absorption of tobramycin is very low when administered by aerosol inhalation, with a limited uptake of the inhaled drug into the systemic circulation, it is estimated that approximately 10% of the mass of drug initially nebulised is

deposited in the lungs and the remaining 90% either remains in the nebuliser, is impacted on the oro-pharynx and swallowed, or is exhaled into the atmosphere.

Sputum concentrations: Ten minutes after inhalation of the first 300 mg dose of Bramitob, the average sputum concentration of tobramycin was 695.6 μg/g (range: 36 to 2,638 μg/g). Tobramycin does not accumulate in sputum; after 20 weeks of therapy with the Bramitob regimen, the average sputum concentration of tobramycin 10 minutes after inhalation was 716.9 μg/g (range: 40 to 2,530 μg/g). High variability of sputum tobramycin concentrations was observed. Two hours after inhalation, sputum concentrations declined to approximately 14% of tobramycin levels measured at 10 minutes after inhalation.

Serum concentrations: The median serum concentration of tobramycin 1 hour after inhalation of a single 300 mg dose of Bramitob by CF patients was 0.68 μg/mL (range: 0.06μg/mL – 1.89μg/mL). After 20 weeks of therapy on the tobramycin regimen, the median serum tobramycin concentration 1 hour after dosing was 1.05 μg/mL (range: BLQ- 3.41μg/mL).

Elimination

The elimination of tobramycin administered by the inhalation route has not been studied.

Following intravenous administration, systemically absorbed tobramycin is eliminated principally by glomerular filtration. The elimination half-life of tobramycin from serum is approximately 2 hours. Less than 10% of tobramycin is bound to plasma proteins.

Unabsorbed tobramycin following tobramycin administration is probably eliminated primarily in expectorated sputum.

5.3 Preclinical safety data

In repeated dose toxicity studies, the target organs are the kidneys and vestibular/cochlear functions. In general, the signs and symptoms of nephrotoxicity and ototoxicity are seen at higher systemic tobramycin levels than are achievable by inhalation at the recommended clinical dose.

In preclinical studies, administration of inhaled tobramycin during up to 28 consecutive days determined modest, unspecific and fully reversible (on therapy discontinuation) signs of irritation in the respiratory tract, and signs of renal toxicity, at the highest doses.

No reproductive toxicology studies have been carried out with inhaled tobramycin, but subcutaneous administration of doses up to 100mg/kg/day during organogenesis in rats was not teratogenic. In rabbits, subcutaneous administration of doses of 20-40mg/kg caused maternal toxicity and abortions, but without evidence of any teratogenic signs.

Considering the data available from animals, a risk of toxicity (e.g. ototoxicity) at prenatal exposure levels cannot be excluded.

Tobramycin was not shown to be genotoxic.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride

Sulphuric acid

Sodium hydroxide

Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products in the nebuliser.

6.3 Shelf life

2 years.

After first opening the single-dose container: use immediately.

In use shelf life: Bramitob bags (intact or opened) may be stored for up to 3 months at not more than 25°C.

6.4 Special precautions for storage

Store in a refrigerator (2-8°C).

Store in the original package in order to protect from light.

The solution of Bramitob single-dose container is normally yellowish; some variations in colour might be observed, which does not indicate any loss of activity if the product has been stored as recommended.

6.5 Nature and contents of container

The medicinal product is supplied in 4ml single-dose polyethylene containers, in sealed foiled bags each holding 4 single-dose containers.

Pack sizes: 4, 16, 28 or 56 single-dose containers.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handlings

For single use only.

Use immediately after first opening the single-dose container. Discard the used single-dose c ontainer immediately.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Chiesi Limited
333 Styal Road
Manchester
M22 5LG
UK

8 MARKETING AUTHORISATION NUMBER(S)

PL 8829/0155

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

26/03/2011

10 DATE OF REVISION OF THE TEXT

24/01/2022